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ORIGINAL INVESTIGATION

C. A. Morgan III · Christian Grillon
Steven M. Southwick · Linda M. Nagy
Michael Davis · John H. Krystal · Dennis S. Charney

Yohimbine facilitated acoustic startle in combat veterans with post-traumatic stress disorder

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Abstract Preclinical and clinical studies have suggested that the acoustic startle reflex (ASR) is a useful model to investigate the neurochemical basis of anxiety and fear states. This work has revealed that the anxiogenic alpha-2 receptor antagonist, yohimbine, increases the amplitude of the ASR in laboratory animals and in healthy human controls. Because of the growing body of data that support the hypothesis that severe stress results in substantial alterations in noradrenergic neuronal reactivity, the present investigation evaluated the effects of yohimbine on the ASR of 18 patients with PTSD and 11 healthy combat controls. Subjects received IV yohimbine (0.4 mg/kg) or saline placebo on 2 separate days in a randomized double blind placebo control design. A trial of two tone frequencies with varied intensity (90, 96, 102, 108, 114 dB) white noise and instantaneous rise time, was delivered binaurally through headphones. Tones were delivered every 25–60 s, for a 40-ms duration. Startle testing was performed 80 min post-infusion and lasted 15–20 min. Yohimbine significantly increased the amplitude, magnitude and probability of the ASR in combat veterans with PTSD, but did not do so in combat controls. Overall startle was significantly larger in the PTSD subjects; however, this did not account for the differential effect of yohimbine, since yohimbine had no significant effect in the control group. This study demonstrates an excitatory effect of yohimbine on the amplitude, magnitude and probability of the ASR in PTSD patients that is not seen in combat controls. In the context of the key role of this reflex in the alarm response, this finding adds to the array of documented behavioral, biochemical and cardiovascular effects of yohimbine in humans which support the relationship between increased noradrenergic function and exaggerated startle symptomatology of PTSD.

Key words Yohimbine · Noradrenergic · Anxiety PTSD

C. A. Morgan III (✉) · C. Grillon · S. M. Southwick
L. M. Nagy · M. Davis · J. H. Krystal · D. S. Charney
National Center for Post-Traumatic Stress Disorder,
West Haven VA Medical Center, 950 Campbell Avenue,
West Haven, CT 06516, USA
Yale University School of Medicine, Department of Psychiatry,
New Haven, CT 06516, USA

Introduction

Clinical investigations focused on elucidating the behavioral and neurobiological changes which occur following severe psychological trauma support the hypothesis that severe stress results in substantial alterations in noradrenergic neuronal reactivity. For example, laboratory investigations in war veterans with post-traumatic stress disorder (PTSD) have consistently demonstrated dysregulation of the sympathetic nervous system. When exposed to combat-associated stimuli such as sounds of gunfire, veterans with PTSD tend to respond with abnormal elevations of blood pressure and heart rate (Pitman et al. 1987).

Similarly, a number of biochemical markers, including increased 24-h urinary excretion of catecholamines, decreased platelet alpha-2 adrenergic receptor number and decreased lymphocyte adenylate cyclase activity are consistent with noradrenergic hyperactivity in traumatized combat veterans (Kosten et al. 1987; Lerer et al. 1987; Perry et al. 1987; Yehuda et al. 1992). Furthermore, medications that act by decreasing noradrenergic transmission such as clonidine and propranolol, appear to diminish arousal related symptoms of PTSD.

A recent study investigating the peripheral and central noradrenergic reactivity in combat veterans with PTSD showed a significantly greater behavioral,

biochemical and cardiovascular response than healthy controls (Southwick et al. 1993). Seventy percent of the PTSD group had a panic attack and 40% experienced a flashback when exposed to the alpha-2 receptor antagonist, yohimbine. In contrast, none of the healthy controls had either a panic attack or a flashback. These results are consistent with alterations in peripheral noradrenergic reactivity, and are suggestive of hyperresponsiveness of brain noradrenergic neurons as a result of severe stress.

Most studies to date have examined peripheral autonomic reactivity and behavioral change, to make inferences about brain function in PTSD. A clearer understanding of central noradrenergic neuronal reactivity might be afforded by using a more direct probe of brain function that is sensitive to noradrenergic neuronal reactivity, fear and alarm states.

The acoustic startle reflex may fulfil such a need. It is measured as a whole body movement in the rat, and as the magnitude of the eyeblink component of the reflex in humans. Its neural pathways have been well described (Davis et al. 1982). Preclinical studies indicate that the startle reflex is increased by fear conditioning and drugs which increase noradrenergic function (Kehne and Davis 1985). In healthy human subjects, startle is significantly augmented by anticipatory anxiety as well as by the anxiogenic, alpha-2 antagonist yohimbine (Grillon et al. 1991; Cook et al. 1992; Morgan et al. 1993). These data provide further evidence for a relationship between noradrenergic hyperactivity, anxiety and alarm states in humans. Examination of these relationships may contribute to a better understanding of the pathophysiology of anxiety disorders such as PTSD.

Recent investigations using a startle test paradigm involving anticipation of electric shock suggest that the startle reflex in combat veterans with PTSD is modulated in a significantly different manner from that seen in healthy control subjects (Morgan, submitted). Because "exaggerated startle" is considered one of the diagnostic features of PTSD, an examination of the neurochemical modulation of startle may provide a clearer understanding of the central neural mechanisms of the anxiety and alarm symptoms seen in PTSD. The present study examines the effect of yohimbine on the amplitude of the startle reflex in combat veterans with PTSD.

Materials and methods

Subjects

Eleven healthy combat control subjects were recruited from responses to advertisements and 18 combat veterans with PTSD were recruited from a specialized inpatient treatment unit. They all gave voluntary written, informed consent for their participation in the study. The combat controls were determined to be free of mental disorders on the basis of the Structured Clinical Interview for Axis I DSM-III-R Diagnoses (SCID), and none of these subjects reported a history of mental illness in first-degree relatives. All subject interviews were administered by a research nurse and reviewed by the consensus diagnosis team (three psychiatrists, two psychologists, two research nurses). The combat control subjects reported not taking any psychoactive medication for the 4 weeks prior to the study. This was verified by urine toxicology screening. The mean age of the PTSD subjects was 42 (±2) years, and the mean age of the controls was 41 (±2). The mean combat exposure scale score of the PTSD subjects was 31.8 (±5.6), which matched that of the combat controls (30.9±6.2). None of the combat control subjects reported a history of serious medical illness, and they all had normal results on physical examination, ECG, and laboratory tests of renal, hepatic, pancreatic, hematopoietic, and thyroid function.

The 18 PTSD patients were diagnosed on the basis of a structured psychiatric interview (SCID). All PTSD subject interviews were administered by a research nurse and reviewed by the consensus diagnosis team (as noted above). Five of the 18 patients had a past and current co-morbid diagnosis of panic disorder, while 15 had a history of prior major depression. None of the patients reported taking any psychoactive medication for the 4 weeks prior to the study. This was verified by urine toxicology screening. In addition to being free of current major depression and psychoactive substance abuse, all subjects were determined to be free of psychotic disorders, and organic mental disorders. None of the patients reported a history of serious medical illness, and they all had normal results on physical examination, ECG, and laboratory tests of renal, hepatic, pancreatic, hematopoietic, and thyroid function.

Procedure

Prior to each test day, subjects fasted overnight for 10 h and remained in the fasting state throughout testing. Each healthy subject participated in 2 test days (yohimbine and placebo). The subjects arrived on the Neurobiological Studies Unit at 8:30 A.M. on each day. At that time, an intravenous line was placed to permit drug administration. A minimum of 2 h after insertion of the intravenous line, yohimbine (0.4 mg/kg) or saline was infused over 10 min. Startle testing began 80 min post-infusion. This study was part of a larger investigation of the biochemical, behavioral and cardiovascular effects of yohimbine which have been reported elsewhere (Southwick et al. 1993). The 80-min delay was required because of the repeated assessments of the behavioral and biochemical effects of yohimbine, that took place before startle testing. In this paper, we report on visual analogue scales completed at baseline and at 60 min post-infusion.

Acoustic startle reflex assessment

Eighty minutes post-infusion the startle response was recorded with a commercially available startle system (SR Lab: San Diego Instruments) in a sound-attenuated chamber. Subjects were seated in a comfortable chair which was kept in an upright position. Audiometric assessment (Welsh Allyn) tested hearing at 500, 1000, 2000 and 4000 Hz. The audiologic exclusion criterion was any hearing loss of more than one frequency band in one ear. No subjects were eliminated on the basis of the audiologic assessment. Unilateral 4000 Hz frequency loss was noted in five of the PTSD subjects and in one control subject.

The eyeblink amplitude was measured by recording the orbicularis oculi electromyographic (EMG) activity with two disc electrodes (Ag-AgCl) placed 1 cm below and 1 cm from the external canthus of the right eye. The ground electrode was placed on the forehead. Impedance was kept below 8 kΩ. EMG activity was

filtered (1–1500 Hz), digitized for 250 ms from onset of acoustic stimuli, rectified, and stored for off-line analysis.

The acoustic stimulus was a 40-ms burst of white noise with a near instantaneous rise time presented binaurally through headphones (Maico). Sets of acoustic stimuli were calibrated with a sound level meter (Realistic) to five intensities: 90, 96, 102, 108, and 114 dB(A). These stimuli were delivered to subjects over a background of 75 dB(A) white noise. Sound was calibrated by means of a 6 cc coupler in an artificial ear (Model EC-9A) and continuous noise.

Recording sessions began 180 s after background noise onset with an initial startle pulse (102 dB), followed by six blocks of acoustic stimuli. Each block was composed of the five intensities presented in a pseudorandomized order every 45–60 s over a period of 15–20 min. Recording sessions ended 15 s after delivery of the last acoustic stimulus.

To analyze the startle reflex, magnitude (inclusion of zero responses) and amplitude (excluding zero responses) were obtained. Because the number of zero responses was high (mainly in the control group at low intensity startle stimuli), the amplitude scores were computed only for the 114 dB (A) intensity of stimulation. The probability of startle was also calculated as the ratio of non-zero responses to the total acceptable trials. The individually scored startle responses were averaged for each drug condition and each intensity of startle stimulus over three successive blocks yielding two data points (blocks 1–3, blocks 4–6) per drug condition, and per intensity of startle stimulus. A preliminary analysis indicated that the two groups and the drug conditions did not impact differently on the startle responses obtained in blocks 1–3 and 4–6. The startle data were further reduced by averaging the startle scores over blocks 1–3 and 4–6.

Statistical analysis

The data were entered into computer files and analyzed using a standard statistical package. Magnitude and probability data were analyzed using a three-way ANOVA with Group (PTSD, Controls), Drug (placebo, yohimbine) and Intensity (90, 96, 102, 108, 114) as the factors. Amplitude data (114 dB A) were analyzed using a two-way ANOVA with Group and Drug as the factors. Reduced degrees of freedom (Greenhouse-Geisser) were used to minimize inflated degrees of freedom and reduce type 1 errors. Note that the degrees of freedom for the three types of measures differ because for the magnitude data: one subject had a missing value at 90 dB. For the amplitude data, two subjects (combat controls) did not have a non-zero response at 114 dB and were not included in the analysis. The initial startle pulse stimuli (102 dB) were analyzed separately using a two-way ANOVA with Group and Drug as the factors.

An analysis of variance was also conducted on the subgroup of five PTSD patients with panic disorder to determine whether or not there were differences in the startle response compared to patients with only a diagnosis of PTSD. Paired *t*-tests were conducted to determine whether and at what time point yohimbine had different effects on these parameters compared to placebo.

The visual analogue ratings of anxiety were analyzed using a three-way ANOVA with Group, Drug and Time as the factors. One PTSD subject, and two control subjects did not complete the ratings and were not included in the analysis.

Results

The magnitude of the first startle response in the combat control group was 61.1 mV (SE = 10.2 mV) and 84.6 mV (SE = 18.8 mV) in the placebo and yohimbine conditions, respectively. In the PTSD group, the corresponding values were 159.1 mV (SE = 49.2) and 216 mV (SE = 27.8 mV). Startle was significantly greater in the patients compared to the controls [$F(1, 28) = 4.6$, $P < 0.04$]. The main effect of Drug and the interaction of Drug × Group were not significant.

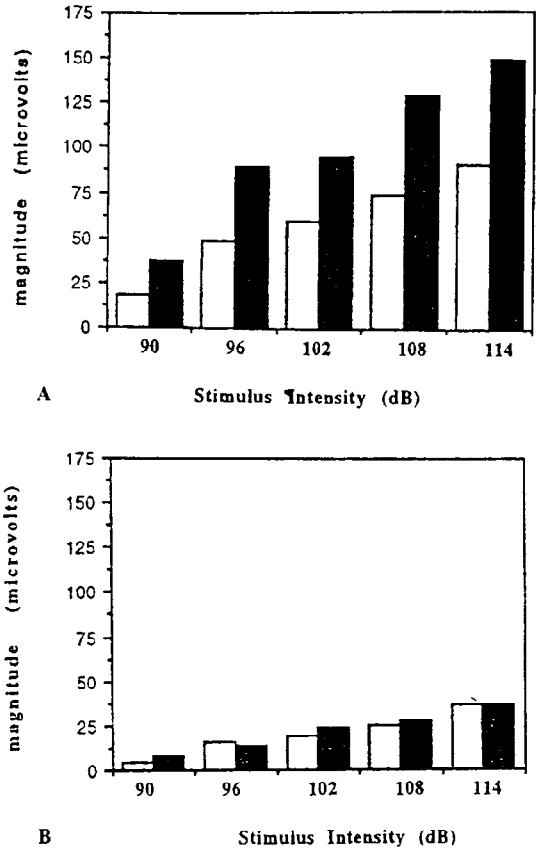

Fig. 1 Effect of yohimbine on acoustic startle reflex (ASR) amplitude in combat veterans with PTSD (A) or combat controls (B). The amplitude of EMG activity of the orbicularis oculi is recorded in microvolts. Subjects received an intravenous infusion of 0.4 mg/kg yohimbine HCl vs. placebo in a randomized, double blind fashion, 80 min prior to startle testing. *Bars* show the ASR amplitude at 90, 96, 102, 108, and 114 dB after yohimbine administration (*black bars*) as compared to placebo (*white bars*). Yohimbine significantly increased startle amplitude at 96,102,108,114 dB compared to placebo ($P < 0.01$, $P < 0.01$, $P < 0.02$, $P < 0.01$, respectively) in veterans with PTSD but not in combat controls. □ placebo: ■ yohimbine

Figure 1 shows the magnitude data averaged over the two blocks. Overall, startle was larger in the PTSD compared to the combat control subjects. Startle was increased by yohimbine in PTSD, but not in combat controls. These results were statistically confirmed. There was a significant Group Main effect [$F(1, 26) = 5.5$, $P < 0.02$] and a significant Group × Drug effect [$F(1, 26) = 6.1$, $P < 0.02$]. Subsequent analysis indicated that yohimbine significantly increased startle in PTSD patients [$F(1, 16) = 12.0$,

Table 1 Mean probability (standard deviation) of startle

	90	96	102	108	114
PTSD placebo	37 (35)	53 (36)	56 (32)	71 (29)	87 (20)
Yohimbine	53 (30)	80 (27)	82 (24)	94 (11)	94 (13)
Controls placebo	19 (31)	53 (37)	46 (37)	57 (40)	66 (28)
Yohimbine	29 (38)	41 (38)	45 (39)	63 (35)	67 (35)

$P < 0.003$] but not in combat controls [$F(1, 10) = 1.1$, $P < 0.3$]. A significant Group × Intensity effect [$F(4, 104) = 4.1$, $P < 0.03$] was also noted, indicating that the difference in startle magnitude between the two groups was greater at higher, compared to lower, intensities.

Table 1 presents the probability data. The probability of eliciting a startle response was greater overall in the PTSD, compared to the combat controls [$F(1, 27) = 5.7$, $P < 0.02$]. Yohimbine had a differential effect on the probability of startle in the two groups (Group × Drug: $F(1, 27) = 4.1$, $P < 0.05$). Yohimbine significantly increased the probability of eliciting a startle response in PTSD subjects [$F(1, 17) = 15.8$, $P < 0.001$] but not in combat controls [$F(1, 10) = 0.01$, $P < 0.9$].

The amplitude measures (see Materials and methods) of the startle reflex to the 114 dB stimulus were the following: PTSD/placebo: 113 μV (SE 22 μV); PTSD/yohimbine: 154 μV (SE 25 μV); Control/placebo: 40.9 μV (SE 13 μV); Control/yohimbine: 43.7 μV (SE 14 μV). Startle was significantly greater in the PTSD compared to the control group [$F(1, 25) = 5.3$, $P < 0.02$]. Yohimbine had a differential effect on these amplitude measures in the two groups (Group × Drug: $F(1, 25) = 5.5$, $P < 0.02$). Yohimbine significantly increased startle amplitude to the 114 dB stimulus in PTSD subjects [$F(1, 16) = 11.2$, $P < 0.004$] but not in combat controls [$F(1, 9) = 0.6$, $P < 0.4$].

The analysis of the subgroup of PTSD patients with co-morbid panic disorder did not reveal any significant differences in the startle response compared to PTSD patients without panic disorder.

Baseline levels of anxiety were significantly higher in the PTSD patients [25.9 (SD 27.2), placebo condition; 28.7 (SD 26.7), yohimbine condition] compared to controls [5.2 (SD 8.8), placebo condition; 7.2 (SD 11.0) yohimbine condition], as reflected by a significant main effect of Group [$F(1, 24) = 9.05$; $P < 0.006$]. However, yohimbine did not produce a significant increase in anxiety ratings from baseline at 60 min in either the PTSD [26.4 (SD 25.8) at baseline; 33.7 (SD 32.7), at 60 min] or the controls [2.7 (SD 4.7) at baseline; 4.3 (SD 6.0), at 60 min]. There were non-significant main effects of Drug and Time, and a non-significant Group × Drug × Time interaction.

Discussion

Consistent with preclinical and clinical investigations, this study demonstrates in humans an excitatory effect of yohimbine on the magnitude of the acoustic startle reflex. However, unlike our previous investigation which demonstrated a uniform and robust yohimbine facilitation of the startle reflex in all subjects, this study shows a significant facilitation of startle by yohimbine in only the PTSD subjects, but not in the age-matched combat controls. It is important to note that the group × drug effect seen in this study is not due to the fact that there are non-startle responders in the control group, for even when zero responses were excluded (amplitude scores), the differential effect of yohimbine in PTSD subjects remains. In addition, this group × drug effect is not a reflection of the difference in baseline scores because within the control group, yohimbine does not have a significant effect. This is an indication that yohimbine affects the PTSD, but not the control group. In the context of the key role of this reflex in the alarm response, this finding adds to the array of documented behavioral, biochemical and cardiovascular effects of yohimbine in combat veterans with PTSD, and supports the relationship between increased noradrenergic function and this disorder.

The facilitation of startle by yohimbine may be due to increased noradrenergic function in the spinal cord. In rats, the yohimbine excitatory effect on baseline startle appears to result from an increase in release of norepinephrine in the spinal cord (Kehne and Davis 1985), which may potentiate the response of spinal motor neurons to afferent stimulation (White and Neuman 1980). Local, selective depletion of spinal norepinephrine blocks the excitatory effect of yohimbine (Kehne and Davis 1985). An increase in norepinephrine release by yohimbine would also be expected to increase the response of facial motor neurons to afferent stimulation (McCall and Aghajanian 1979). This effect should facilitate the eyeblink component of startle which is medicated by facial motor neurons.

Several investigations have provided support for sympathetic nervous system dysregulation in patients with chronic PTSD (Shalev et al. 1992; Southwick et al. 1993). It is thought that the effects of yohimbine are mediated through its ability to increase presynaptic noradrenergic activity by antagonizing the alpha-2 adrenergic autoreceptor (Charney et al. 1984, 1987,1992). An abnormal sensitivity of spinal or brainstem presynaptic noradrenergic neuronal reactivity in the PTSD subjects may be responsible for the facilitation of startle seen in this study. The suggestion that the yohimbine facilitation seen in the PTSD subjects is due to a neuronal site of action in the spinal cord rather than a non-specific fear or anxiety potentiation is

supported by the lack of a yohimbine-induced increase in anxiety at the time of startle testing. Further, the increased startle response in PTSD patients during both placebo and yohimbine conditions compared to controls suggests that the startle response may be independent of the influence of cortical noradrenergic projections and of amygdala projections and may support the hypothesis of unconditioned physiologic responding in PTSD (Shalev et al. 1992).

Because clinical investigations have indicated that subjects with panic disorder also show increased physiologic responses to yohimbine administration (Charney et al. 1984,1987,1992), it is possible that the facilitation of startle in the PTSD patients was due to the subgroup with co-morbid panic disorder. However, this is unlikely, because the analysis of this subgroup failed to show significant differences from the rest of the patient sample.

It is noteworthy that in its response to yohimbine, the startle reflex of PTSD subjects is more like that of younger healthy subjects (Morgan et al. 1993) than that of age-matched combat controls. Preclinical data suggest that the startle reflex normally diminishes with age (Davis, personal communication). It is possible that the lack of a significant yohimbine effect on the startle reflex in combat controls is due to a diminution of the modulatory mechanisms of the reflex caused by the aging process.

Historically, and by DSM-III-R criteria, one of the features of PTSD is exaggerated startle. Of four published objective studies investigating startle in PTSD (Ornitz and Pynoos 1989; Ross et al. 1989; Butler et al. 1990; Shalev et al. 1992), only one demonstrated exaggerated baseline startle in a subgroup of combat veterans with PTSD (Butler et al. 1990). In the current study, the amplitude (excluding zero responses) and magnitude (including zero responses) of the startle response PTSD subjects and in combat control subjects differ significantly in the placebo condition. These data provide evidence in favor of "acquired" exaggerated startle in PTSD. It is possible that the stressful nature of the IV drug challenge generalized to the experimental context in which the startle testing occurred. This would be consistent with the mechanism of shock sensitization. An alternative hypothesis is that the increased startle seen in the PTSD subjects is due, in part, to anxiety. It is possible that their higher anxiety ratings reflect a significant level of anticipatory anxiety or contextual arousal about the test procedure which facilitated the startle response. Thus, the exaggerated startle seen in this disorder may be strongly influenced by contextual arousal.

In laboratory animals, yohimbine increases the magnitude of fear-potentiated startle (Davis et al. 1979). Investigation of this effect in veterans with combat related PTSD may prove to be a method capable of more definitively assessing the relationships among noradrenergic function, startle responsiveness, and conditioned and unconditioned responding.

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